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## THE PLACE OF FORMATION AND THE FUNCTIONAL PRINCIPLES OF CONDITIONED CONNECTIONS

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The primary conditioned reflex may be considered as a chronic or stable product of higher nervous synthesis of two congenital reflexes, possessing specific peculiarities which differentiate it from both unconditioned reflexes and from such related, more primitive, purely transient and volatile phenomena in the activity of the nervous system as a *Bahnung*, a summation reflex and a dominant. Among the most pertinent problems of higher nervous activity, which have attracted keen attention, beginning with the origin of the theory of conditioned reflex activity up to the present day, are the following: (a) Which part of the central nervous system is the centre of conditioning and the organ of conditioned reflex activity? (b) Which shifts in the functional state of the nerve centres underlie conditioning and what functional peculiarities of the nerve cells are responsible for these shifts? (c) Which structural shifts in the body of the nerve cells and of their processes make up the material groundwork of a conditioned connection?

I. P. PAVLOV's views on all these points are well known.

(4) Some contemporary investigators have voiced the opinion that the capacity for conditioning is inherent not only in the higher and central parts of the central nervous system in highly-developed organisms, but supposedly also in its lower parts, namely the spinal cord (SHARRAGER, COLLIER *et al.*).

The erroneousness of conceptions of this kind in relation to the so-called spinal conditioned reflexes has been demonstrated through the experiments by our associates T. N. NESMEYANOVA and N. M. SHAMARINA, which have been reported previously. They have shown under conditions of acute and chronic experiments on dogs in which the spinal cord was dissected at the level of the last pectoral segments, that first of all, as a result of a multiple combined electrical stimulation of the tail and of one of the hind paws of a spinal animal, a whole complex of diverse, aberrant and variable reflex reactions is formed, caused both by separate stimulation of each of these organs and by stimulation of other areas of the body, innervated by the caudal half of the dissected spinal cord, and not a unilateral reflex response of one and the same type as recorded in the similar experiments by SHARRAGER, COLLIER *et al.* They have also found that exactly the same result can be obtained during a multiple repeated stimulation of only one of these organs, without combination with others, *i.e.*, when the formation of a genuine conditioned reflex is quite ruled out. These atypical reflex reactions also differ from a conditioned reflex by the dynamics of their formation. In full contradistinction to the dynamics of formation and specialization of the conditioned reflex, these atypical reactions are of a local nature at the beginning of their formation and subsequently, as the number of stimulations increases (simultaneously of the tail and of the paw, or of only one of the organs), they become increasingly generalized, and the zone and assortment of the reflex reactions caused during the application of testing stimuli is extended.

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If one also adds to this the fact that these reactions are, as a rule, of short duration and of a volatile nature, it will become evident that they belong to the phenomena of the VEDENSKY 'hysteriosis' type, and do not have the rank of a conditioned reflex. Apparently the development of higher stationary excitability in the nerve structures of a dissected spinal cord underlies such atypical reflexes, and this development greatly facilitates the diffuse spreading of excitation emerging in any of its points. This is also demonstrated by new experiments conducted by T. N. NESMEYANOVA in which she has shown that if the trophic and reflex activity of the caudal section of the animals' spinal cord is maintained in a good condition for a short while after its dissection by means of regular massage, training and stimulation of the hind extremities, the atypical reflexes appear in this case by themselves as a natural manifestation of such a condition and are maintained for a long time.

Somewhat different is the case of possible conditioning by various subcortical nerve formations. According to the results obtained in the laboratories of Y. P. FROLOV, D. A. BIRYUKOV, A. I. KARAMYAN, I. G. VORONIN, A. B. KOGAN, the author of this paper, ROTAR, BOKOV, MILYUTINA *et al.* it is possible to elaborate primitive skeletal-motor and especially diverse vegetative conditioned reflexes in laboratory experiments in higher fishes, reptiles and birds, i.e., in animals practically devoid of the cerebral cortex, as well as in rodents with the cerebral cortex removed by a surgical operation. The question still remains open whether the nearer or remote subcortical nerve formations of higher vertebrates are capable of elaborating at least primitive conditioned reflexes. The new facts relevant to this point, presented by M. N. PANKRATOV, Y. N. BELENKOV, M. A. NUTSUBIDZE and Ts. A. ORJONIKIDZE, as well as the corresponding former data collected by G. P. ZELENY and his associates, cannot be regarded as unquestionable proof of the existence of such a capacity either on account of insufficient removal of the cerebral cortex in their experimental animals or because of the extreme instability and non-specificity of the reactions formed in these animals. On the other hand, other investigators, including the associates of our laboratory, have never succeeded in elaborating food, acid- or electro-dentensive reflexes in dogs completely devoid of the cerebral cortex. The reactions so formed in such animals are very short-lived, they are preserved for hours or for days at best and are characterized by the typical properties of the Bahnung-dominant phenomenon. For example, in the experiments conducted by our collaborator T. N. RYABOVA in some decorticated dogs, after prolonged repeated electrical stimulation of one of the paws, whether in combination with diverse kinds of indifferent stimuli or without it, it was possible to create a condition of higher excitability of the elements of the corresponding reflex arc during which spontaneous movements of the paw become more frequent and intense, while outside stimuli, particularly tactile and acoustic ones acquire the property of strengthening or provoking them anew. Such conditions are most frequently created at the end of each experimental course and disappear by the following experimental day. In rare cases such conditions are maintained for a day or even for several days. Such data cannot, however, serve as a basis for explicitly ruling out the possible conditioning, however primitive, by the subcortical and intermediate brain formations of normal higher animals, since, as a result of surgical decortication of the brain, substantial degenerative changes take place in these formations. As to the statements made recently by GASTAIT, FESSARD and others to the effect that conditioned reflexes are elaborated in the reticular formation of the brain stem to be projected later on in some mysterious way into the cerebral cortex, their groundlessness is so evident that, judging from available information, the authors have now themselves renounced them. The new reliable facts on this matter, obtained with the aid of electrophysiological methods, in full conformity with the former abundant material supplied by PAVLOV's and his disciples' laboratories, clearly indicate that in highly-developed animals the cerebral cortex is the organ for elaborating and implementing the most perfect, complicated and highly conditioned reflexes, as far as the level of development is concerned.

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Judging from all available facts, a conditioned connection between two points of the cortex can be established both transcortically, through the subcortical long nervous conducting pathways and through the subcortical nuclei and bodies. This is notably borne out by the following data which we obtained previously, and which have recently been confirmed by N. N. DZIDZISHVILI, O. S. ADRIANOV, G. N. MERINO and M. M. KHANASHVILI. With a complete surgical separation of the occipital, temporal and frontal lobes of both hemispheres of the brain, it is possible to elaborate electro-defensive motor conditioned reflexes to acoustic and optical stimulations: these reflexes disappear after subsequent extirpation of the separated anterior part of the cortex. It is quite probable that the changes in the pattern of electrical activity of some specific and non-specific subcortical formations during conditioning, found by a number of researchers (GASTAUT, FESSARD, HERNANDEZ-PEON, MORRELLI, TROPIMOV and his associates, RUSINOV and his associates, LIVANOV and his associates, etc.) are to a considerable extent an expression of the participation of these formations in the process of closing the conditioned connection between two points of the cortex as intermediate links between them.

(B) As to the second of the above questions, PAVLOV held the view that the closing of a conditioned connection is functionally based, first of all, on the general neurophysiological phenomenon of the summation reflex or *Bahnung* and, secondly, on the extreme reactivity and impressiveness inherent in the cells of the higher parts of the central nervous system, the properties owing to which the momentary and volatile phenomenon of a summation reflex is fixed in these parts as a chronic phenomenon, i.e., a conditioned connection.

Recently Soviet and some foreign researchers have obtained new facts on this subject which permit us to define more accurately the functional shifts in nervous sites when a conditioned connection between them is closed.

First of all, one should stress the considerable rise in excitability of the nerve elements of combined stimulus 'sites', which occurs in the course of conditioning and which is a major prerequisite for the closing of conditioned connections. Although many facts can be found in the old experimental material of PAVLOV's laboratories, testifying to such changes in the functional condition of the central nerve structures during conditioning, this question has, nevertheless, become the object of special investigations quite recently, and it is precisely in these investigations that the above phenomenon has been revealed in a most distinct form. For instance, Soviet investigators A. M. MARUSEVA, L. A. CHISTOVICH, A. A. GYURJIAN, A. I. PSHONIK, and F. A. FELBERBAUM, N. Y. ALEXEENKO, and S. M. BLINKOV, E. N. SOKOLOV *et al.* and others have established on people that after an indifferent stimulus becomes conditioned, the threshold of the reaction to this stimulus undergoes a considerable and stable diminution, i.e., sensitivity to it substantially rises. A similar fact has been established in experiments on animals, partly by means of electrophysiological methods (E. M. KRIPS, N. I. LAGUTINA, N. I. NIKOLAYEVA, GALAMBOS, JOUVET, HERNANDEZ-PEON *et al.*). This well-established fact quite definitely bears out that conditioning is attended with a stable rise in excitability of the nerve structure of the brain, corresponding to the stimulus. The same phenomenon, and in the same illustrative form, has been ascertained with regard to the nerve structures of the brain, corresponding to a reinforcing or an unconditioned stimulus. It has been shown by the experiments carried out by K. S. ABULADZE, N. I. NIKOLAYEVA and our associates L. I. CHILINGARYAN, E. A. ROMANOVSKAYA *et al.* that elaboration of both salivation and motor electro-defensive reflexes is accompanied by a sharp rise in the excitability of cortical structures corresponding to an unconditioned stimulus. It is noteworthy that in the experiments of the last three investigators this change has been disclosed by directly determining the level of excitability of the appropriate cortical points through a direct testing stimulation by electric current by means of chronically implanted electrodes. It is of interest that the development of a steady rise in the excitability of these

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structures precedes the appearance of the conditioned reflex; the latter emerges after the excitability of the structures has reached a certain, rather high level. This important fact becomes clearly prominent in both ABULADZE's experiments on salivation reflexes and in the experiments conducted by NIKOLAYEVA, CHILINA and ROMANOVSKAYA on electro-defensive motor reflexes. Further, it is shown that the lowered threshold of excitability of the nerve elements of a fixed localization, and according to preliminary data of our collaborators, in the nature of the electrical activity of these elements. It is evident that the substantial stable rise in the excitability of cortical structures, corresponding to a reinforcing stimulus, is an indispensable requisite for the emergence of a conditioned connection. It is worth adding that according to the data collected by our associates M. E. VARGA and Y. M. PRESSMAN, who are determining the level of excitability of nervous structures of both the signal and reinforcing stimuli in their experiments aimed at elaborating conditioned reflexes, that in a bilateral connection, the excitability of the nervous structures of the second stimulus rises to a higher level than that of the structures of the first stimulus. When the sequence of applying stimuli is altered, i.e. when they change places, the level of excitability of the nerve structures of the former reinforcing stimulus (which has now become a signal stimulus) is somewhat lowered, and that of excitability of the nerve structures of the former signal stimulus (which has now become reinforcing) undergoes a rise.

It is hardly possible to analyse here in detail the question regarding the probable mechanisms of these changes in the level of excitability of the conditioned and unconditioned 'site' nerve elements. It is, however, worth stressing the great likelihood of similarity between the mechanism of this phenomenon and that of the same phenomenon, namely, the rise in excitability and the intensified activity of the peripheral neuromuscular apparatus and spinal nervous structures, resulting from their prolonged and methodical activation, known since SCHIFF's and VEDENSKY's time and subsequently termed 'post-tetanic potentiation' and recently thoroughly studied by ECCLES, LLOYD, P. G. KOSTYUK, our collaborator N. V. VESBA *et al.* Apparently the higher level of excitability of these sites is responsible for the interaction between them (as unilateral or counter irradiation of excitation or in some other way) during their direct or reflex excitation which gives rise to a conditioned connection. A higher level of excitability of the reinforcing stimulus site as compared with that of the signal stimulus excitability is evidently due to the fact that the reinforcing stimulus site is excited both by a signal stimulus and its own stimulus, while the signal stimulus site is excited by its own stimulus only. A rise in excitability of the central nervous structures resulting from their activation, as well as the physiological importance of this phenomenon, is also most vividly manifested in the emergence and the course of the Bahnung, summation reflex and dominant phenomena, kindred to the conditioned reflex. It is well known that these phenomena, developing in the higher part of the central nervous system, make up, as it were, the first phase in the formation of a conditioned connection and, at any rate, they play an important part in this case. This clarifies the significance of the new facts established by some Soviet scientists, M. N. LIVANOV, V. S. RUSINOV, N. V. GOLIKOV, A. B. KOGAN, A. I. ROITBAK *et al.* to the effect that conditioning is also accompanied by some other changes in the functional state of the nerve elements of combined stimulus 'sites', typical of these general neurophysiological phenomena, particularly of the dominant, their highest form. These are expressed in a considerable rise in the lability of the nerve elements and in their enhanced capacity for recruitment of a present rhythm and synchronization of activity of the nerve elements inside the given 'site', as well as for synchronization of activity of different 'sites', and a substantial inertia in maintaining the occurring changes. Judging from all available facts, these functional shifts in the nerve elements of the higher parts of the central nervous system are manifested in a more vivid form than in those of the underlying parts of the system.

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(C) As to the question regarding the fine structural and physico-chemical shifts in the nerve tissue, which constitute the material basis of a conditioned connection, PAVLOV, who had no direct facts at his disposal, confined himself to the hypothetical assumption that shifts in the finest ramifications of the nerve cell processes or in the dividing membranes between them (i.e., in the formations known in modern science as synapses) might be regarded as such a basis of a conditioned connection. An identical viewpoint, or one close to it, is shared by a number of contemporary neurophysiologists, KONORSKY, ECCLES, BERITASHVILI *et al.* It is assumed in this case that the closing of a conditioned connection is due either to the formation of new synapses or the activation of existing potential synapses, or to an increase in the surface of the synapses as a result of their regular activation. Very alluring is ECCLES' hypothesis to the effect that post-tetanic potentiation is due to plastic changes in the synaptic apparatus, namely to the swelling of the synaptic button, to protoplasmatic shifts in it, to an increase in its volume, as a result of this, to a contraction of the synaptic slit. It is possible that the 'extreme reactivity and impressiveness' of the nerve cells of the higher parts of the central nervous system precisely reduces itself to their pronounced capacity for such plastic changes.

In summing up the above statements regarding the structural and functional principles of the closing of a conditioned connection, it is worth noting that PAVLOV'S initial theoretical propositions that conditioned reflexes are elaborated by the higher parts of the central nervous system and that higher excitability and excitation of activated nervous sites play an important role in closing a conditioned connection have been fully confirmed and further developed in recent electrophysiological investigations. His hypothesis that the closing of a conditioned connection is itself effected by the cells of the higher parts of the central nervous system in the areas of the dividing membrane, i.e., of the synaptic contact between these cells, owing to their inherent properties of extreme reactivity and impressiveness, despite its distinctly hypothetical nature still remains the most convincing one.

# **ELECTROPHYSIOLOGICAL STUDIES DURING THE FORMATION OF A TEMPORARY CONNECTION**

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The electrophysiological data obtained in the investigations of higher nervous activity in the past five or six years were the subject of discussion at a number of international conferences and colloquia: the Marseilles Colloquium in 1955<sup>14</sup>, the Fourth International Congress on Electroencephalography in Brussels in 1957<sup>14, 15</sup>, and the International Colloquium in Moscow in 1958<sup>16</sup>. In addition, a number of researchers have devoted detailed reviews to this matter<sup>1, 17</sup>. Some of these dealt with the materials published before 1960. All this greatly facilitates our task and permits us to concentrate on the subject which has in recent years attracted ever widening attention on the part of investigators. I am referring to the slow lasting changes in the potential of the cerebral cortex and their relation to the function of the closing of a temporary connection.

Slow lasting changes in the potential of the cerebral cortex have been recorded in a number of cases (ARDUINI *et al.*<sup>1</sup>, BROOKHART *et al.*<sup>2</sup>, BURES<sup>4</sup>, GOLDING and O'LEARY<sup>3</sup>, SHVETS<sup>18</sup>, ALAJALOVA<sup>1</sup>, MORELL<sup>11</sup>, MNUKHINA<sup>19</sup>, and others).

From our point of view, slow lasting oscillations of the potential, like its fast oscillations, reflect the process of excitation, but of one that is manifested in its other form, namely as stationary excitation. Such a view presupposes the existence of lasting sites of excitation in the central nervous system as normal and significant factors of its activity, the sites being reflected by slow lasting potentials. Such a conception also presumes that essentially both the activity current and the slow lasting potential are related to an active physiological condition.

ARDUINI *et al.*<sup>1</sup> have shown that lasting changes in the potential are extensively observed along the cerebral cortex during stimulation of the reticular formation of the mid-brain. This potential is of neuron origin since it is considerably increased in amplitude by a local application of strychnine and completely disappears in the case of nembutal. According to BROOKHART *et al.*<sup>2</sup>, negativation during a stimulation of thalamic specific nuclei is confined to a certain area of the homolateral cortex, while during a stimulation of the intralaminar nuclei of the thalamus it is observed in both hemispheres, the maximum negativation being in the frontocentral regions. Stimulation of the reticular formation of the mid-brain differs from that of the medial thalamus as it involves a larger region, spreading to the parietal and occipital regions.

It has been shown in T. B. SHVETS' work<sup>18</sup> that lasting slow potentials in the cerebral cortex of rabbits are observed during the elaboration of defensive conditioned reflexes to light. The first few applications of afferent stimuli (light, sound) cause a depression of the basic rhythm of the EEG without any noticeable shifts of the steady potential level. With the extinction of the orienting reaction, the stimuli (light, sound) no longer cause any distinct changes in EEG. Individual applications of an unconditioned stimulus result in a momentary depression of the basic rhythm of the EEG. But neither

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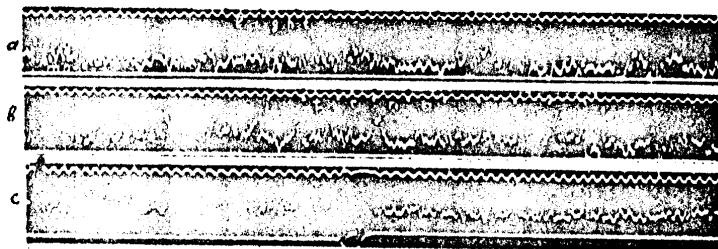


Fig. 1. EEG of a rabbit's optical region. Direct current amplifier. Non-polarizing electrodes. Orienting reaction to light and sound extinguished. Light (A), sound (B) and electro-cutaneous stimulations (C) do not cause any slow shift of the steady potential of the cerebral cortex. 1 - recording of respiration; 2 - EEG; 3 - recording of movement. Time mark - 1 sec.;  $\downarrow$  = beginning of stimulation;  $\uparrow$  = end of stimulation.

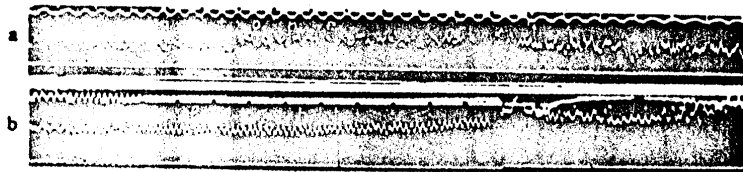


Fig. 2. EEG of the optical region of the same rabbit. Phase of generalization. A - indifferent stimulus (tone) like the conditioned stimulus (light) B - causes a shift of the steady potential of the cerebral cortex. Negativity corresponds to a shift upwards.

conditioned stimulus nor an unconditioned one, when applied separately, brings about a shift of the steady potential of the cerebral cortex (Fig. 1).

After the very first combination, light as well as electro-cutaneous stimulation begins to provoke a depression of the basic rhythm of the EEG. The following should be stressed as being of special importance: after three to ten combinations, in response to a conditioned stimulus only (light), a recording appears in the cerebral cortex of a slow shift of the steady potential as a lasting negative or positive oscillation of the potential. These lasting oscillations have a latency ranging from two to five seconds and an amplitude from 100 to 400 (and more) microvolts. The shift of the steady potential in the optical and motor regions increases drastically after an unconditioned reinforcement, up to 600 to 700 microvolts and then gradually diminishes, without reaching its former level for a long time. As the number of combinations increases, the changes in the level of the steady potential become less pronounced, apparently because of the process of concentration. Fig. 2 shows the EEG of a rabbit's optical region, recorded in one of the first few combinations of light and an electro-cutaneous stimulation. The conditioned stimulus caused a slow shift of the steady potential level. An indifferent stimulus (tone) likewise brings about a shift of the steady potential level in the phase of generalization (Fig. 2a). Subsequently, as the temporary connection and the elaboration of differentiation become stabilized, the slow lasting oscillations of the potential expressed in a shift of the cerebral cortex steady potential appear to a conditioned stimulus only, and not to a stimulus to which differentiation has been elaborated.



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It has been found by ARDUINI *et al.*<sup>8</sup> in acute experiments on animals and on preparations with an 'isolated brain' that repeated stimulation of afferent nerves results in the appearance of a slow lasting potential which is extensively spread along the cortex. On the other hand, in chronic experiments on an intact animal, notably during the formation of a temporary connection, slow lasting potentials appear in the cerebral cortex in response to all stimuli during the phase of generalization and, when the reflex is strengthened, only to the stimulus which has acquired a signal importance.

Lasting oscillations of the cortical steady potential level are not themselves peculiar to the formation of temporary connections. They reflect the existence of a stationary excitation with its oscillations of a lasting nature. Distinct oscillations of the steady potential level, in response to afferent stimulations, appear where conditions are provided for the emergence of a stationary excitation and the appearance of some level of negativity: a dominant focus, foci during conditioning, and protracted stimulation in exposed areas of the cortex in an acute experiment. They may also appear 'spontaneously' under the same conditions, in response to afferent stimulations from the external or internal environment of the organism, which are not taken into account by the experimenter.

At the same time the experiments point to a major role of electrotonic influences, which are reflected electrographically in the shape of lasting slow potentials, in forming temporary connections. Lasting slow potentials which appear to reflect one of the forms of functional inter-neuron connection, characterize most adequately the functional condition of the structure from which they are recorded. It is not accidental that an increasing amount of data is accumulating, which points to the fact that the amplitude and shape of practically all the potentials recorded from the surface of the cerebral cortex depend on the level of the steady potential of the cortex.

Electrotonic influences are similar to the action of a direct current. By polarizing the cerebral cortex and the subcortical structures with a weak direct current, it is possible to set up artificially in the cortex the shift of the steady potential level which is formed during the natural emergence of a temporary connection in the case of conditioning. G. D. KUZNETSOVA has found that polarization of the surface of a rabbit's cerebral cortex in the area of the cortical end of the motor analyser with an anode using a weak direct current (current density 0.8 microampere per mm<sup>2</sup>.) causes regular shifts of the cortical steady potential level. The magnitude as well as the direction of these shifts proved to depend on the initial level of the potential of the cortex: negative deviations were observed when the cortex was more positive, and vice versa, if the cortex was slightly negative; it tended, in the main, to become positive after the direct current effect.

A number of experiments were performed to study the effect of a weak direct current on the cortical end of a rabbit's motor analyser both in acute and in chronic experiments<sup>11, 22</sup>.

The results of the research indicate that polarization of the cortical end of a motor analyser at the point of representation of one of the paws with the anode of a weak direct current (from one to five microamperes) creates conditions under which afferent stimulations (light, sound), to which an orienting reaction has been previously extinguished, bring about a motor reaction of the animal's corresponding or most corresponding extremity. The data have been confirmed by MORRELL<sup>12</sup>. A more detailed survey of investigations carried out with direct current was outlined in the *Journal of Higher Nervous Activity* in 1961<sup>13</sup>.

The motor effect of an afferent stimulation remains for some time after the direct current has been switched off. The time is variable. The maximum time of its preservation did not, however, exceed 20 to 30 minutes in acute experiments, and two to three hours in chronic ones. In some experiments the motor reaction of the extremity corres-

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ponding to the point of polarization in the cortex was observed to afferent stimulations on the following day after the direct current had been switched off.

In polarizing various layers of a rabbit's cerebral cortex, RYABININA<sup>10</sup> found that the minimum current required to obtain a threshold motor response of an extremity to an afferent stimulation was recorded when the tip of the electrode was in the fifth layer. But the electrode has to be connected to the cathode, and not to the anode as in experiments with the polarization of the cortex surface. When an electrode whose tip is in the fifth layer of the cortex is connected to an anode, the motor effect of the afferent stimulation is inhibited. Histological checking has confirmed that the tip of the electrode is located precisely in the fifth layer of the cortex.

Of special interest for grasping the physiological mechanisms of the function of temporary connection closing are the data showing that the sites of excitation, set up by polarization with a weak direct current in the cerebral cortex, preserve for some time the rhythm preset for them.

R. A. PAVLYGINA stimulated the cortical end of a rabbit's motor analyser with a weak direct current which, along with a constant component, had a sinusoidal one of a varying period (pulsating current): three oscillations per second or one oscillation per two to 8 seconds. Polarization itself with a pulsating current did not provoke any motor reactions. Movements of the extremity arose only in response to afferent stimulations (light, sound, tactile) applied during the polarization. *These movements took place at the rhythm of the pulsating current.* This phenomenon is easy to inhibit. It suffices to intensify the direct current acting on the cortex, and they disappear. Inhibition is proved by the reaction of 'rebound' in the form of intensified reflex movements to the same afferent stimulations after switching off the direct current. The more lasting the inhibition, the greater the resulting movements during the 'rebound'. *During the period of 'rebound', after the inhibition, the rhythm of contractions corresponds to the frequency of the previously applied pulsating current.* In other words, during inhibition in the central nervous system, the rhythm predetermined by the experimenter still remains in a latent state in the focus set up in the cortex by the weak direct current, and it may manifest itself after inhibition.

The still greater importance of electrotonic influences for the formation of temporary connections can be seen from the facts which indicate that in chronic experiments the focus set up in the cortex with a weak pulsating current remains for several days. In other words, after one day of experiment, reflex movements with a period corresponding to that of a pulsating current can be obtained when applying afferent stimulations, without applying the pulsating current to the cortex.

In his 'Glia-neuron theory of brain function'<sup>11</sup>, analysing the published data on the effect of direct current on the cerebral cortex, and especially the capacity of a weak direct current for changing the functional state of neuron activity for a long period, R. GALAMBOS considers that these facts directly related to the closing of temporary connections cannot be explained only by the changes occurring in the membrane of the neurons. He regards glia and neurons as jointly acting functional units and advances the assumption, in common with a number of other researchers, that glia cells are quite possibly responsible for the slow waves. GALAMBOS' theory is far from being actually substantiated, but it may prove useful for further investigation into the functions of the brain.

Using microelectrodes in the optical area of a rabbit's cortex, MORRELL<sup>12</sup> has shown that when recording the electrical activity of individual neurons, it is also possible to disclose the recruitment of a predetermined rhythm under the influence of a weak direct current. In his experiments some neurons discharged with a single burst of impulses to every flash of light. In applying a weak direct current on the cortex and using flashes

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of light at a rhythm of five per second he later found that this rhythm also existed in the case of a single flash; this time the neuron responded not with a single burst but with a train of them at five per second. This phenomenon remained for up to 20-30 minutes in MORRELL's experiments. This time coincides with the one obtained in acute experiments during the formation of an excitation focus in a rabbit's cerebral cortex under the influence of a weak direct current<sup>14</sup>.

Investigating the morphological peculiarities of changes in tissue structural elements of rabbits' central nervous system during the implantation of electrodes (constantan wires, from 150 to 170 microns in diameter insulated to their tips), M. M. ALEXANDROVSKAYA has demonstrated the phasic pattern of morphological changes, depending on the time after the implanting of the electrodes. Observations were carried on for 45 days after the implantation. Even after only a few days an alteration occurs both along the electrode channel and at the end of the electrode with the appearance of lymphocytes, fibroblasts and glial elements. Then the site of alteration begins to resolve actively with the aid of glial cells (microglia) and the whole process terminates in a development of gliosis at the end of the electrode and a general diffuse reaction of microglia in the brain. As mentioned by ALEXANDROVSKAYA, it is noteworthy that changes in the tissue structural elements of the brain after the implantation of electrodes are limited owing to the activation of neuroglia cells which are responsible for the resorption of the injured tissues without forming cicatrices. An extensive mobilization of astroglia and particularly of microglia is observed. The reaction of astrocytes is of a more local nature, while microglia produces a diffuse reaction in the parts of the brain more remote from the electrode.

The fact that a great number of glial cells accumulate at the end of the electrode implanted in the brain recalls the data presented by TASAKI, CHANG *et al.*, who have shown that astrocytes in a culture of tissues, generate a slow electrical activity in response to stimulation. An astrocyte in a culture of a tissue in the experiments performed by HILD *et al.*<sup>15</sup> produced an 'electrical response', lasting over a thousand times longer than the action current of nerve cells in the same culture. TASAKI and CHANG<sup>16</sup> cited data which indicate that glial cells in mammals' cerebral cortex are likewise capable of producing an electric response to a direct stimulation. They inserted an ultramicro-electrode in a cat's cortex and recorded the slow reversible changes in the potential, resembling 'electric responses' from glial cells in a culture of a tissue.

These data raise many new problems in the physiology of the central nervous system, particularly in the field of investigation into the physiological processes underlying the mechanism of formation of temporary connections.

In recent years mathematics has penetrated into every branch of research, including that of work on the brain. Of all the work in this direction, reference should be made to the investigations carried out by GELFAND and TSETLIN 'The principle of non-local search in the systems of automatic optimization' and others<sup>17</sup>, which, in their deductions pertaining to physiology, are close to the views we have advanced on the role of lasting slow potentials in the function of the brain. It is of interest and apparently not incidental that mathematicians, proceeding from their solutions of the problem of automatic optimization with a great number of working parameters, and physiologists, proceeding from their viewpoints regarding the various types of functional inter-neuron connection, supported by experimental data with polarization of the cerebral cortex, are in essential agreement regarding the considerable, though not decisive role for the higher functions of the brain of those processes which are reflected electrographically by lasting slow potentials.

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# THE SPECIFIC ASCENDING ACTIVATION AS A PHYSIOLOGICAL BASIS FOR THE FORMATION OF THE CONDITIONED REFLEX

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As soon as the physiological peculiarities of the reticular structure of the brain stem were discovered, neurophysiologists were forced to examine a number of new problems of cortical-subcortical relationship (MORUZZI and MAGOUN, 1949; MAGOUN, 1950; JASPER, 1949).

The most important of these problems was *how to qualify* the new form of arousal spreading through the channel of the central encephalic system and greatly differing as to its physiological properties from the arousal effect spread through the 'classical' lemniscus system.

There were weighty reasons for posing these problems. Our established concepts on the spreading of excitations through the central nervous system, formed before the discovery of the physiological properties of the reticular structure, proved inconsistent.

We supposed that excitations, generated in response to external or internal stimuli, are spread from this initial point, frequently on the linear principle, over an ever expanding territory. It seemed evident that the energetic resources required for this spreading were drawn directly from the spreading excitation in every consecutive point of the central nervous system.

This concept, according to which primary excitation is selfsupplied with energy along the whole line of its spreading, has also been proved to be inadequate.

The discovery of the physiological specificity of the reticular structure of the brain stem has had a particularly great influence on our conception of the associative activity of the cerebral cortex. According to this conception the presence in the cortex of 'two points of excitation', originated by an irritation of the lemniscus system, seemed quite sufficient to make the associative connection between them.

The simple fact of obtaining evoked potentials *in the state of narcosis* (FORBES, 1932) was the first actual proof of the inadequacy of these conceptions, founded on the idea of the existence of one lemniscus-thalamic system of excitation. This deduction could have been made even at that early stage, but was not arrived at then.

The research conducted by MORUZZI and MAGOUN and the systematic research later made by JASPER and other scientists showed that the cortical effect of external stimulation is a more complicated formation than was admitted before in neurophysiology.

This was the origin of the first classification of ascending activations into 'specific' and 'nonspecific' (MAGOUN, 1950, 1958). The most characteristic symptoms of nonspecific activations were: (a) absence of sensory modality, (b) activated character (desynchronization) and (c) generalized spreading over all the cortex.

This first classification was founded on the assumption that the 'nonspecific' nature of activation is a *universal* and *homogeneous* property of every ascending activation of the cortex. In short, it was assumed that nonspecific activation, produced by the ascending excitations from the reticular structure, is the same for all kinds of cortical activation manifested by the desynchronization of its electrical activity. And all the types of

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generalized desynchronization of cortical activity were naturally admitted to be also equal, not differing from each other in any of their physiological qualities.

The systematic research carried out in our laboratory showed that this concept of a single type of activation influence on the cortex was likewise inadequate and required considerable broadening.

The very first experiments made by V. AGAFONOV, who applied pain activation under urethan narcosis, discovered certain new aspects of the ascending activating influences on the cortex. By causing nociceptive irritation on the hind limb of a rabbit he obtained several unexpected results (V. AGAFONOV, 1956).

Although the animal was actually in a narcotic sleep, its electric activity showed a sharp activation (desynchronization) of cortical electrical activity.

It was evident to us that this was the first indication that urethan, as a narcotic, possesses special properties. This proved to be the lucky chance owing to which we were in a position to doubt, as early as 1959, the physiological truth of the conception that ascending activation has a certain universality and single form.

I shall try to reproduce the logical thread of argument which later led to a series of specially directed experiments.

In the first place we were forced to admit, on the strength of numerous experiments published by that time, that the state of wakefulness is, in itself, an *activated* state of the cortex, which gets this activation from the rostral part of the reticular structure of the brain axis (MAGOUN, 1950).

At the same time, every new stimulus, exercising its influence in the wakeful state, immediately causes supplementary activation in the form of a sharply defined generalized desynchronization of electric activity in the wakeful state (orienting-investigatory reaction).

But, in an animal or man who is awake, pain irritation also causes the sharp desynchronization of cortical electric activity, due to the ascending activation which reaches it.

We have therefore three types of ascending activating influence on the cortex, all of them manifested by the generalized desynchronization of cortical electric activity, differing only by the degree of activation.

If all three types of activation had the same physiological quality and the same nervous substratum, we ought to infer that urethan, as a narcotic, must also block all these types of activation.

But, as we have seen, it represses the activation of wakefulness and the activation of tentative-experimental reaction, leaving the activation of pain untouched.

We have, therefore, in this case *different chemical specificity of the nervous substratum of three different activating influences on the cerebral cortex.*

What is the actual substance of this selective action of urethan on the different activating mechanisms of the subcortical apparatus?

The most likely supposition seemed to be that *this selective sensitivity to urethan is connected with the different chemical nature of the different biological complexes of the subcortical structures: the hypothalamus and the reticular structure.*

On the strength of this conclusion we turned our attention to the comparative study of ascending activations of the cortex with a definitely different biological origin. Such activities, differing as to their biological qualities, are known to researchers. They are: the conditioned reflexes to food and defence against pain.

These experiments have been reported at several international conferences (ANOKHIN, 1959, 1960) and in a special report delivered at the Pavlov session devoted to higher nervous activity, which was arranged jointly by the Academy of Medical Sciences of the USA and the New York Academy (P. K. ANOKHIN, 1961).

The numerous experiments of my colleagues—A. SHUMILINA, V. GAVLICHEK, I. ZYCHINAYEVA, Y. MAKAROV and others—have shown that chlorpromazine (aminasin) in definite doses has a selective blocking effect only on the defensive states and defensive

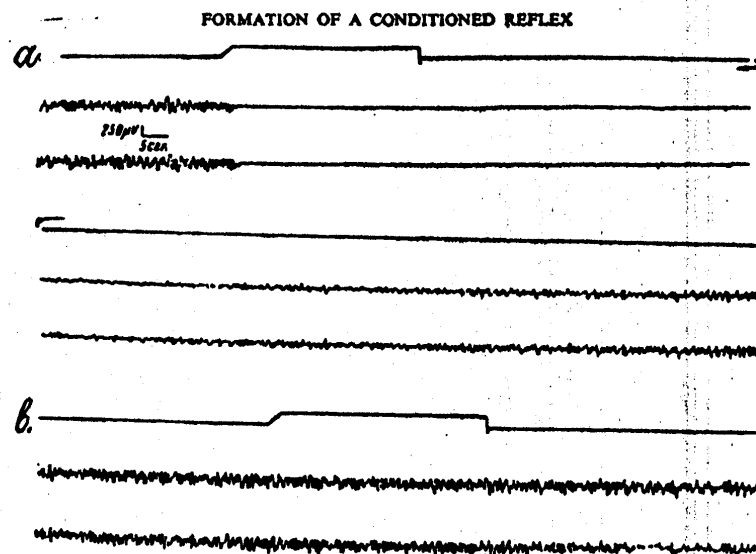


Fig. 1. (a) Shows the action of the nociceptive stimulus under urethan anaesthesia. The stimulus evokes remarkable generalized desynchronization of the electrical activities of the cerebral cortex. (b) The same stimulus does not cause desynchronization in the cortex.

conditioned reflexes of the rabbit, leaving the conditioned food reflexes in substance unchanged.

Chlorpromazine correspondingly blocks defensive ascending activation and leaves food activation free to manifest itself (A. SHUMILINA, 1956; V. GAVLICHEK, 1958, 1959; I. ZACHINAeva, 1960; Y. MAKAROV, 1960).

Here we are faced, in principle, with the same phenomenon of selective influence as in the case of urethan, but in a demonstratively reciprocal aspect: chlorpromazine blocks selectively the mechanisms of ascending activation by pain, leaving the mechanisms of wakefulness and food activation untouched.

We conducted experiments to ascertain the level on which chlorpromazine begins to block pain activation selectively. We adopted, as a characteristic symptom of pain activation of the cortex, the rise of blood pressure which always accompanies it and sharp changes of the motor rhythm. The experiment was made on a decerebrated cat (according to SHERRINGTON). The rise of blood pressure and quickened breathing disappeared immediately after an injection of chlorpromazine in the decerebrated cat.

These experiments showed that, from a specific and chemical point of view, the substratum blocked by chlorpromazine lies in the rostral part of the reticular structure of the stem.

The absence of conditioned defence activation (desynchronization) on the cortex surface, after the injection of chlorpromazine, must therefore be interpreted as the result of loss of ascending activation from some substratum which is sensitive to chlorpromazine and insensitive to urethan.

All these facts, as well as the conclusions to be drawn from them, have led us to formulate the conception that every activating influence on the cortex is specific. However, this activation is specific in relation to the biological quality of the given act.

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*in general (food, defence, tentative, etc.) and not in relation to some sensory modality.*

This specificity is particularly apparent in case of the pharmacological dissociation of different types of biological activity in animals.

We recently obtained an additional demonstrative example of the biological specificity of ascending activating influences on the cortex in the experiments of our colleague V. SUDAKOV.

It is well known that a cat sleeping under narcosis (urethan, nembutal) all the areas of the cortex show the slow electrical activity typical for the somnolent state.

But if the cat is starved some days before the experiment, the picture of electrical activity of its cortex undergoes a marked change. While the temporal, parietal and occipital areas of the cortex show the slow activity usual for the sleeping state, the frontal areas of the cortex, on the contrary, show a clearly different activity of the arousal effect type.

The fact that the special activity of the frontal area is connected with the state of starvation, induced by the narcotic substance, i.e., is manifested in the somnolent state, requires attention to this activity, and requires thorough experimental analysis.

We have shown, if this activity is the result of excitation of the food centre of the brain, i.e., by 'starved blood' (ANAND and BROBECK; ANDERSON; BROBECK), then the change from 'starved blood' into 'satiated blood' must lead to the appearance of the usual slow activity in the frontal areas.

Satiation of a starved cat under urethan or nembutal narcosis was accomplished by two methods: introduction of milk through the mouth and oesophagus into the stomach, with particularly marked irrigation of the mouth cavity, and intravenous injection of a glucose solution.\* These methods were intended to imitate as near as possible the natural process of satiation which, as we have shown, is composed of several factors (P. K. ANOKHIN, 1962).

Our calculations proved right. Immediately after the process of 'satiation', the activated state of the frontal areas of the cortex changed to the slow electrical activity characteristic for the somnolent state. Though this slow activity was not entirely similar to the electric activity of the other areas of the cortex, it differed radically from the activity corresponding to the starved condition.

We must stress that the whole process of 'satiation', i.e., the process of replacing the electric activity of the starved cat by the electric activity of the 'satiated' cat, developed under narcosis, against the background of a deeply somnolent state.

These experiments leave no doubt that the independence of ascending activations of starvation of the frontal areas of the cortex from the somnolent state and narcotic blockade has a profound biological meaning. It is probably this physiological peculiarity of the activation described above that wakens the hungry animal from sleep and sends it in search of food. We evidently have it also in the behaviour of the infant who wakes only to receive food.

Now we have very interesting additional facts.

As well known from our previous experiments urethan anaesthesia does not block the painful activation of the cortex. On the contrary, chlorpromazine blocks that activation, even under urethan anaesthesia. And finally, the ascending activation of the frontal lobes caused by hunger is not blocked by urethan anaesthesia.

This naturally immediately arouses a very significant question: would chlorpromazine block simultaneously both ascending activations—by pain and by hunger?

Our recent experiments have shown that chlorpromazine blocks selectively painful activation only, but does not at all affect activation by hunger of the frontal lobes under urethan anaesthesia.

This new evidence shows us that in this particular case we also have several species of quality of ascending activations and their selective action on the cortical cells.

\* See Figures 5 and 6, page 897.



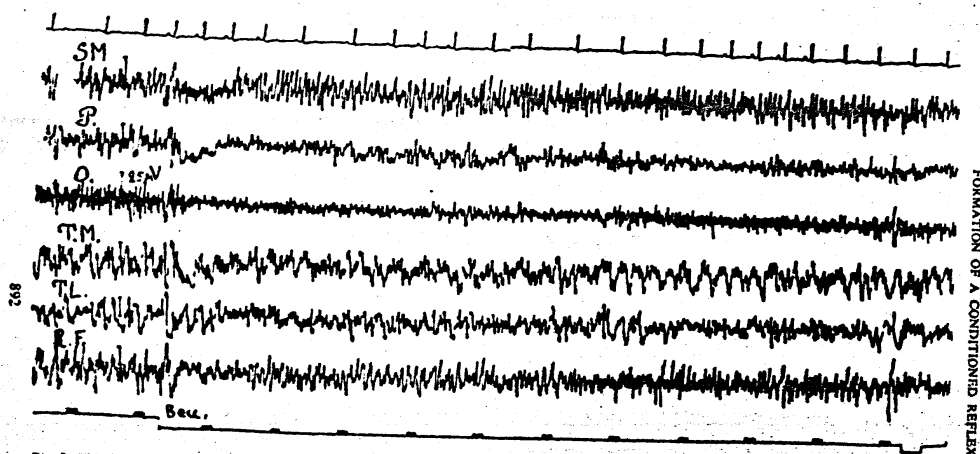


Fig. 2. This figure shows the desynchronization corresponding to the orienting response of cortical electrical activities following the conditioned stimulus after chlorpromazine action.

Abbreviations: SM — Sensory motor cortex  
P — Parietal cortex  
O — Occipital cortex  
T.M. — Thalamus medialis  
T.L. — Thalamus lateralis  
R.F. — Reticular formation

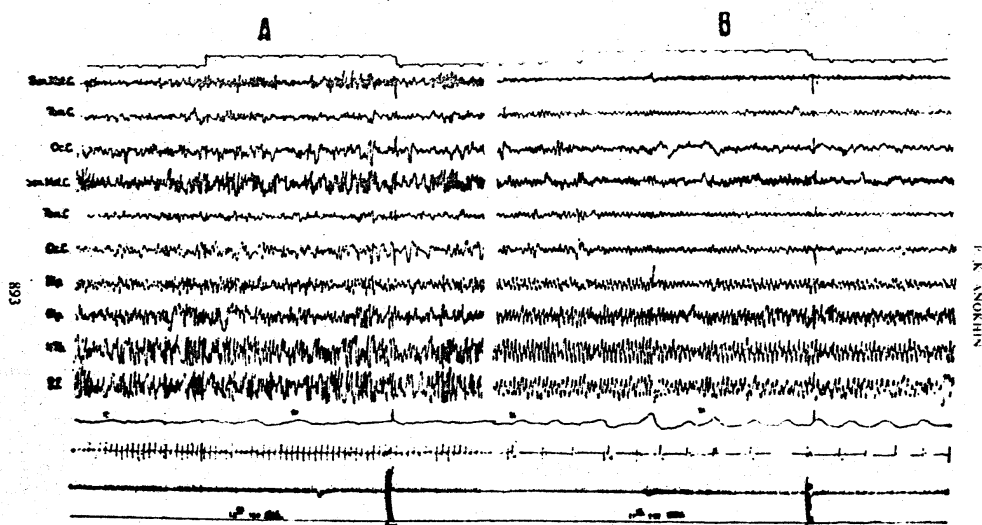


Fig. 3. Change of electrical activities of cortex as influenced by different chemical stimulations.  
 (a) after injection of chlorpromazine (aminasin). Conditioned stimuli do not affect the desynchronisation.  
 (b) within one minute after the injection of adrenaline the permanent generalisation of electrical activities of stress-character is seen.

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It is reasonable to assume that all the above mentioned ascending influences spreading from different subcortical energetic points of different functional systems converge to the same cortical neuron but only through different and specific synaptic connections.

Nevertheless, this special problem remains to be studied at some future time.

The example of local hunger activation of the cortex stresses the exceptional physiological variety of ascending influences of the cerebral cortex and adds reality to our conception of *specific and selective* ascending influences on the cortex.

From this point of view, any complicated form of activity of the whole organism possessing a biological quality (the 'functional system' according to our terminology) forms a single restricted cortical-subcortical system, specific for that given species of activity.

We are convinced by experimental material that the biological quality and purely energetic unity of the whole cortical-subcortical system are maintained by the subcortical structures. In other words: it is a system whose individual links have a heterogeneous physiological importance.

Our experiments provide sufficient ground for admitting that every cortical-subcortical system of that kind is heterogeneous also in respect of the selective chemical sensitiveness of its individual links in relation to the activity of different pharmacological substances.

The fact that *two decisive physiological properties of each of these systems of activation of cortical activity and highly selective sensitiveness to chemical agents, belong to the same subcortical links of the system*, is a remarkable feature of these cortical-subcortical systems.

This was clearly shown, for example, in the selective blocking of cortical pain desynchronization by the intravenous injection of chlorpromazine, or in the selective activation by the hypothalamus of the frontal areas of the cortex, i.e., the state of 'starvation'. Chlorpromazine blocks the activity of the subcortical links of the extensive cortical-subcortical system, which have an activating importance for all the remaining parts of the system, so that, naturally, *the whole system of cortical-subcortical interaction which maintains the state of fear is disintegrated*.

It follows that, to eliminate the activity of any widely branched functional system of the organism, integrated on the level of cortical-subcortical interaction, it is not at all necessary to block *all the links* or all the components of the system. The very nature of the brain's integrative activity is such that it is sufficient to eliminate (block, repress) the links of the system that maintains energetic unity of the functional system and this functional system, with all its definite physiological or biological qualities, will then cease to exist as a whole.

At the present time such a point of view seems to me quite right and it is largely proved by experiments.

Moreover, any general conception of the nature of a phenomenon is always more acceptable if it explains in the most plausible way the factual material collected by that time. Our point of view on the physiological peculiarities of specific and selective ascending influences allows us to give this explanation of several physiological problems.

We can take, as an example, the selective therapeutic effect of 'psychotropic' substances, especially 'tranquilizers', which forms the basis for a new trend in medicine, called 'psychopharmacology'.

We have, by now, abundant experimental and clinical data which convince us that substances having a psychotropic effect have an exceptional specific and selective effect on definite forms of psychic disease (HIMMICH, 1957; MILLER, 1960).

We are trying to work out an explanation of the physiological mechanism of their action on various psychic states.

It is hardly likely, for instance, that the basic point of this explanation must be the effect of these substances on the elementary processes of the nervous system—excitation and inhibition (MORUZZI, 1960).

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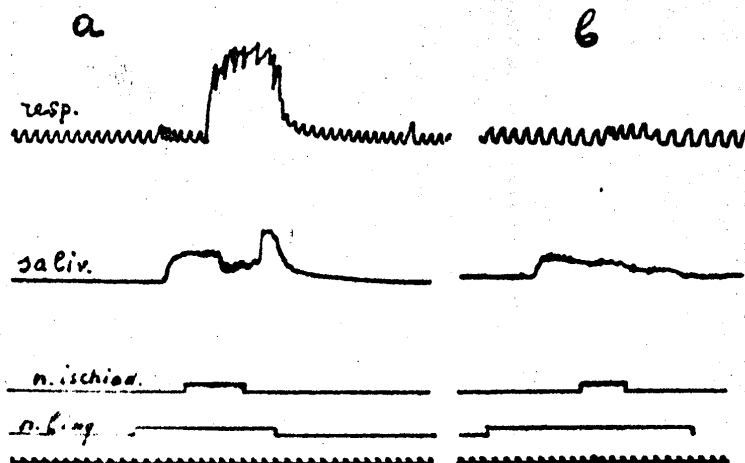


Fig. 4. Influence of chlorpromazine on reaction to pain stimulus of decerebrated cat (stimulation of the sciatic nerve).  
 a. Before injection the remarkable respiratory reaction is seen.  
 b. After injection the respiratory reaction has disappeared.

There is no doubt that any drugs introduced in the blood will, *in the end*, influence the processes of excitation and inhibition. But this alone does not explain why these substances should influence these two processes developing in a given physis state, nor why that physis state is eliminated selectively a whole in all its numerous components and systems of excitation and inhibition.

As I ponder over the factual material relative to this problem, I become more and more convinced that all psychopharmacological effects can be explained in a much more acceptable way on the basis of the architectural principle, *i.e.*, by the properties of a widely branched functional system with components that are heterogeneous from a chemical and physiological point of view.

From this point of view we may take it that the state of anxiety or fear is caused by the existence of a selectively organized system of nervous connections between the cortex and subcortex. This system is built in such a way that a great amount of associative accumulations refer mainly to the cortex. On the other hand, energetic facilitation, which ensures the selective contact between many elements of the cortex, that is practically the maintenance of this branched system in the integrated and dominant state, is undoubtedly caused by the corresponding subcortical structures ('Emotions—the source of power of the cortical cells', according to PAVLOV).

It is therefore quite natural that every dominating system of relationship disappears as soon as its chemically most vulnerable link is blocked. It is vulnerable owing to maximum energetic potencies and consequently tense metabolic processes.

Figuratively speaking, the tranquilizer builds, 'prepares', the whole functional system from numerous integrative structures of the whole brain, leaving other functional systems in a more or less normal state.

The psychopharmacological effect is not the only phenomenon in the activity of the whole brain which can be easily explained on the strength of our conceptions of the specific character of ascending activating influences on the cortex. The differentiation

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of the conditioned reflexes of a different biological nature are undoubtedly formed and defined on the same principles.

Figuratively speaking, by means of the selective blockage of the most energetic and vulnerable links of the functional system, the tranquilizer 'pulls out' the given functional system from numerous integrative systems of the whole brain, leaving other functional systems in a more or less normal state.

In several special cases those last non-blocked functional systems may appear in very accentuated expression, for instance, the appearance of greedy eating after injection of chlorpromazine and after disappearance of permanent anxiety ('release phenomenon') (GAVLICHEK, 1958).

Suffice it to say that the complete elimination of the defence system and its cortical superstructures and simultaneous maintenance of clearly manifested food reactions after the injection of aminasin (chlorpromazine) is a sufficient example of this law (V. GAVLICHEK, 1958; P. K. ANOKHIN, 1961).

There is one point in the above mentioned conception which cannot yet be precisely established; on it depends the further cognition of the *mechanisms of realization* of ascending activating influences at the level of the cortical cells. In examining the mechanisms of the selective spreading of the excitations over all the cortical synapses, we always bore in mind the well established fact that the primary point of selective chemical effects of pharmacological drugs are the subcortical structures phylogenetically differentiated to chemical sensitiveness. We admit that the excitation originated here by specific chemical trigger mechanisms spreads in an ascending direction up to and including the cortical nervous elements.

But an important question arises: is there any chemical difference in the synaptic endings of the cortical cells and in the subsynaptic membrane cells responsible for the realisation of the ascending activations of different biological origin?

And is there no correspondence between the chemical qualities of the synapses of the cortical and subcortical level in the same functional system?

We cannot answer these questions yet, though the answer must certainly be very important to the cognition of the integrative activity of the whole brain.

We can only note that a considerable part of the ascending synaptic contacts at the cortical level are undoubtedly formed in the prenatal or early postnatal period on purely morphological principles, consolidated by heredity (D. PURPURA, 1960; ARA-MURADOVA, 1960).

Their chemical properties are therefore undoubtedly determined hereditarily and we may admit, on phylogenetic principles, a certain chemical peculiarity of these synaptic contacts. The great variety of these chemical processes in the synapses has been recently shown in a comparative physiological aspect by H. GRUNDLER (1961).

Very detailed material has recently been provided by BULLOCK, who showed that the membrane of the same cortical cell is not wholly homogeneous. On the contrary, it has varied properties, both chemical and physical, in different areas of the cellular body (BULLOCK, 1959).

For example, some sections of the membrane have a very low threshold of sensitive ness and can therefore be the generators of nervous impulses, while other points do not possess these properties. There are also grounds for speaking of the different chemical properties of different synapses. The division of synapses into 'depolarizing' and 'hyperpolarizing' is only a first step towards this chemical differentiation.

In this connection I should like to draw your very special attention to a very interesting observation made by our laboratory and closely connected with the question under discussion.

As is well known GABA blocks the depolarizing synaptic connections and leaves unchanged the hyperpolarizing one. This classification is based on the purely ph

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signs of the nervous processes. It is assumed that physical features are only one symptom for cognition of the state of the membrane of the nervous cells.

Nevertheless, several observations with GABA action lead us to doubt whether all the depolarizing synapses have the same metabolic nature.

We have shown that the usual negative component of the primary evoked potential, after application of GABA, really disappears but a new negative component with longer latency immediately appears.

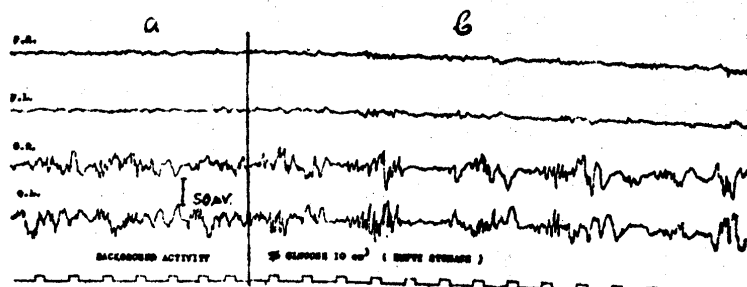


Fig. 5. (a) Demonstration of different electrical activities in different areas of cortex of a starving cat under urethan anaesthesia.

The two upper recordings taken from frontal areas show the desynchronisation.

b) Slow electrical activities have appeared in frontal areas after injection of glucose.

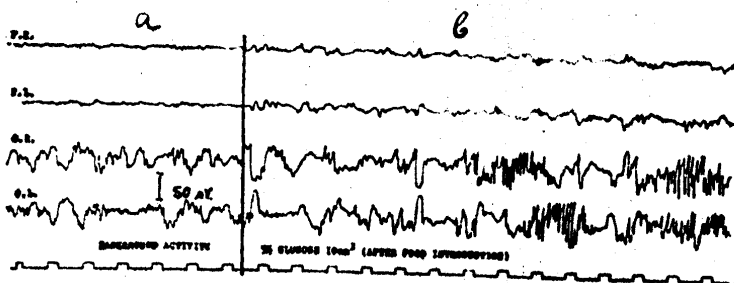


Fig. 6. The same conditions as in the previous experiment, but instead of glucose milk was injected into the stomach by means of a rubber tube. More expressive slow electrical activities are seen.

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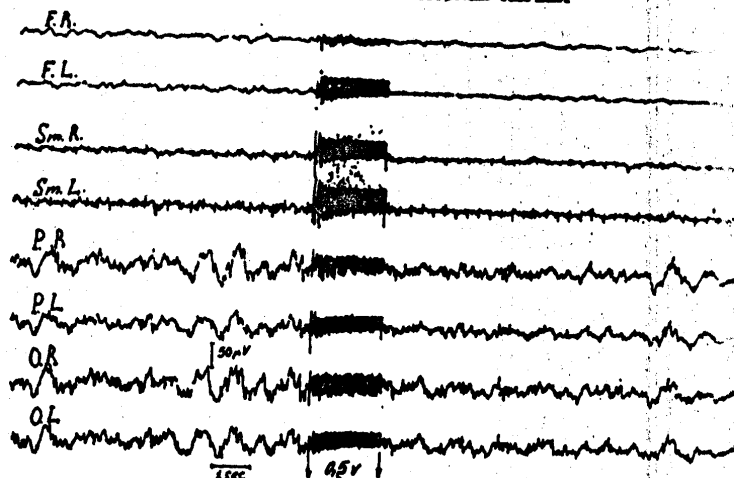


Fig. 7. The recording demonstrates different sensitivity of feeding and painful substrate subcortical areas.

(a) After injection the desynchronized activities are seen in the frontal areas.

(b) The painful stimulation does not provoke desynchronisation in other areas of the cortex.

Thus, actually we have two negative potentials which are identical from the electrical point of view, but are quite different in their metabolic basis.

That is probably why the first negative potential is blocked by GABA while the second one escapes from its chemical action.

This problem will, in any case, be studied experimentally with the greatest care. Should it appear that individual synapses of the cortex have a chemical variety in some degree corresponding to the chemical properties of the subcortical synapses, the whole study of the problem of specificity and selectiveness of ascending activations would acquire an extremely interesting direction.

POOR ORIGINAL

## SPATIAL ANALYSIS OF THE BIOELECTRIC ACTIVITY OF THE BRAIN

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Many attempts at spatial analysis of the brain biopotentials have been performed by using toposcopic equipment (GOLDMAN and associates, LILLY and CHERRY, WALTER and SHIELDS, McDERMOTT, COOPER and MANDY-CASTLE, and others. Our experiments have likewise been conducted by electroencephaloscopic methods. The electroencephaloscope provides 50 or 100 parallel recordings with a transmission from 2 to 70 cycles per second. The device has been constructed according to the switching principle. It supplies at the output a spatial light mosaic of biopotentials with the luminous points on the screen of the electron-beam tube located in accordance with the location of the pick up electrodes on the surface of the brain. In addition, by means of simultaneous linear scanning the quantitative values of the potentials of all the points are recorded as columns of a corresponding height. With electrotoscopic methods, an opportunity has been afforded for investigating simultaneously the bioelectrical mosaic of the cerebral cortex in animals and man under various functional conditions. A number of regularities have been revealed in the spatial course of diffuse bioelectrical processes. A stereotypy of these processes has been disclosed, as well as the existence of specific figures, distribution of the reliefs of biopotentials in the cerebral cortex, the direction and speed of their displacement, etc. Secondly, there appeared the opportunity of studying strictly local isolated phenomena investigation of which was formerly impeded because it was impossible to examine simultaneously the biopotentials of the whole surface of the cerebral cortex. These focal processes, the so-called local high-amplitude oscillations of the potential, reveal a number of interesting functional relationships. There is reason to believe that they reflect the uneven changes in the level of the constant potential of neuron structures. Investigations were conducted in the laboratory of such phenomena under various conditions (sleep, alert state during the applications of different stimuli and pharmacological tests in a normal and a pathological state). Results were also obtained on neurosurgical and neuropsychiatric patients. It has been shown that changes occur in the cortical mosaic in cases of tumours of various localizations, of epilepsy, of different forms of schizophrenia, etc.

It is impossible to consider in a brief lecture all the above aspects of spatial analysis of biopotentials, and we have only concentrated our attention on the problem of analysing the synchronism of biopotentials.

The electroencephaloscope supplies such a large amount of information that its processing calls for special methods. Therefore, to analyse the synchronism, we followed FARLEY and his associates (1957) and TENTURI (1959) in using computers. This work was performed by the staff of our laboratory, namely T. A. KOROLKOVA and G. D. KUZNETSOVA, in association with the scientific worker of the Institute of Electronic Controlling Machines, E. V. GLIVENKO.

We investigated the correlation in pairs of the bioelectrical activity of all the 50 or 100 points at our disposal. Coincidence of the direction of the changes in the potentials



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from moment to moment for every pair of derivations served as a criterion of potential similarity.

To this purpose an appraisal of the sign (+, —, 0) of the first derivative of potential in regard to time was first made for every recording. Then for every pair of recording a comparison was made on the computer of the signs of the derivatives from moment to moment for a fixed time period, and the percentage of coincidences of the derivative signs was calculated. This corresponded to an approximate calculation of correlation for two selected derivations.

We confined ourselves to measuring the film obtained when photographing at a speed of 24 frames per second. It follows from this that we took into account the changes in the potential, within a range from 40 to 500 milliseconds.

As a result of the calculating operations, we obtained a tabulation table consisting (in the case of derivations from 50 points) of 1225 figures, each of them defining the degree of similarity of a corresponding pair of derivations during a selected time period. Proceeding from the tabulation table so obtained, it is possible to plot distribution curves.

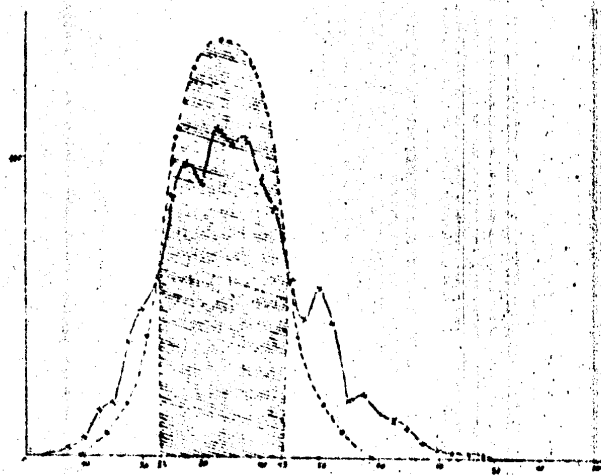


Fig. 1. Distribution curves.

The solid line denotes the distribution curve obtained in the analysis of background biopotentials of one rabbit's cortex in one experiment (the biopotentials were derived by the averaged method). The dotted line denotes the theoretical distribution curve.

Fig. 1 shows a distribution curve obtained as a result of analysing the biopotentials of a rabbit's cortex (solid line), and the theoretical curve of distribution (dotted line). The percentages of coincidences (from 0 to 100) are plotted along the abscissa, and the number of pairs of points working with the given percentage of similarity, along the ordinate.

The theoretical curve of distribution was obtained for the case when the potentials in every derivation follow their course independently and may undergo changes in three directions. Provided the likelihood of each of the three changes being equal, the maximum of this curve should amount to 33% of similarity.

By comparing the experimental distribution curves with the theoretical curve, it is possi-

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ble to separate in the experimental material the independently working points from the interconnected ones and to appraise the degree of the interconnection. The hatched section is made up of the independently working points. The more sloping course of the right shoulder of the experimental curve indicates the existence of a certain group of points with a positive interconnection. The more sloping course of the left shoulder indicates the existence of points with a negative interconnection between them, which is the case when they work in anti-phase.

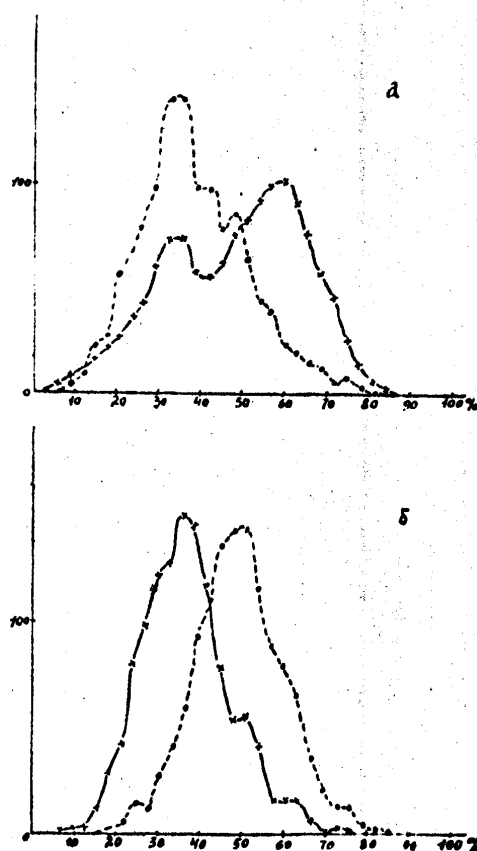


Fig. 2. Distribution curves.

- a. Distribution curves obtained in the analysis of background biopotentials of a rabbit's cortex, recorded by the monopolar method (solid line) and by the averaged method (dotted line) in the same experiment. (Duration of the length analysed: 1.5 sec.)  
 b. Distribution curves obtained in the analysis of background biopotentials of a man's cortex, recorded by the monopolar method during a proper (solid line) and improper (dotted line) location of the indifferent electrode.

## FORMATION OF A CONDITIONED REFLEX

We analysed the distribution curves obtained when applying various methods of biopotential derivation.

Fig. 2 shows the distribution curves obtained in the same experiment by the monopolar method of recording biopotentials (solid line) with the indifferent electrode placed on the nasal bones and by the averaged method (dotted line), when the potential under every electrode is measured in relation to the average level under the rest of the electrodes. The difference between these curves is quite distinct. Thus, the group of positively interconnected points is far more pronounced in the case of the monopolar method of derivation, while positive interconnection is weaker during the application of the averaged method. At the same time negative interconnection, e.g., antiphase relation between the biopotential oscillations, is well pronounced in this case, while it is not found in monopolar derivation. What accounts then for such a difference?

The large positive interconnection during monopolar derivation may result from the influence of the potential arising at a reference point. This potential will tell on each of the 50 points increasing their similarity. But with the existing influence from the indifferent electrode, the maximum of independent points on the distribution curve during monopolar derivation should shift to the right as compared with the maximum on the distribution curve during an averaged derivation. Coincidence of the maxima of the distribution curves when both methods of derivation are used precludes the possibility of accounting for the existence of a great number of points with positive interaction during monopolar derivation by influence from the indifferent electrodes (see Fig. 2a).

Monopolar derivation appears to record correctly the processes of synchronization of the cortex. The cases in which a low-grade indifferent electrode was used can always be detected by the displacement of the maximum of independent points on the distribution curve, and this method is an adequate criterion for constant control over the quality of the indifferent electrodes (see Fig. 2b).

Proceeding from statistical results, it may be assumed that the difference in the above distribution curves is related to a distortion caused by the averaged recording.

There is no zero value on the 'averaged electrode'. The value of the potential on it may differ, depending on the number of interconnected points and on the amplitude of their potential.

The absence of zero on the 'averaged electrode' results in the averaged derivation approximating the bipolar one, and this should inevitably lead to some distortion of the electroencephaloscopic pictures.

It can be seen from the above that distribution curves allow an appraisal of the advantages and shortcomings of the various methods of derivation.

The use of computers for spatial analysis of the synchronous activity of the various points of the cortex among them has shown that several forms of synchronization can be singled out in rabbits in an alert state.

The results can be presented as spatial topographic pictures directly indicating which points of the cortex interact synchronously at a given time interval. It appeared that the foci of the greatest synchronism may be classified into two principal groups.

The first is the zone of compact synchronism, i.e., those cases when the interacting points are located close to one another (see Fig. 3a).

The second is the zone of synchronously acting points, spatially divided and some times far apart from one another. This is a case of distant synchronism (see Fig. 3b).

Besides these two most common types of synchronous structures, more complex forms of interrelations are revealed. For instance, the compact structure may either become distinctly separated from the surrounding sections which work independently in relation to it (see Fig. 3a); or there exists a gradual transition from the section into

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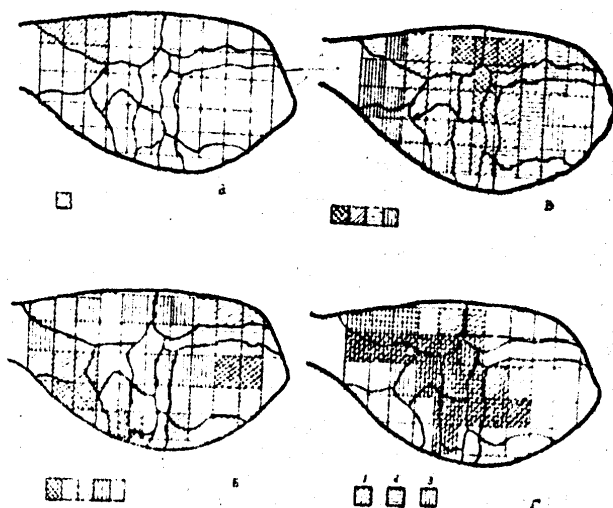


Fig. 3. Examples of structures.

- a. Compact;
- b. Distant;
- c. With a gradient;
- d. Interstratified (of three structures).

The boundaries of the cytoarchitectonic fields according to Rose (1931) are plotted in the contour of the left hemisphere. The location of each electrode corresponds to each square.

The hatched sections correspond to the location of the structures in Figs. a, b and c. Different hatching denotes a dissimilar degree of biopotential correlation.

Double slanting hatching: from 100 to 80%;

Single slanting hatching: from 80 to 60%;

Horizontal hatching: from 60 to 50%;

Vertical hatching: from 50 to 23%;

No hatching: below 23%.

In Fig. d different hatching denotes the existence of three structures, each of which has a synchronism of about 70%.

of which the points work with maximum synchronism to the zones with a gradual drop in the percentage of synchronism (Fig. 3c).

Several synchronized structures, independent of one another, may also be present simultaneously in the cortex. Such individual structures may be either sharply delimited from one another, or possess gradual transitions resulting in the formation of intermediate sections which can be classified functionally as belonging to the second or even to several structures (Fig. 3d).

The action of casual light or sound stimuli deranges the constellations of background activity.

A study has been made of the changes in the synchronism of oscillations of biopotentials at various points of rabbits' cerebral cortex during the elaboration of conditioned reflexes.

A defensive conditioned reflex was elaborated in two rabbits on a stimulation stereo-

## FORMATION OF A CONDITIONED REFLEX

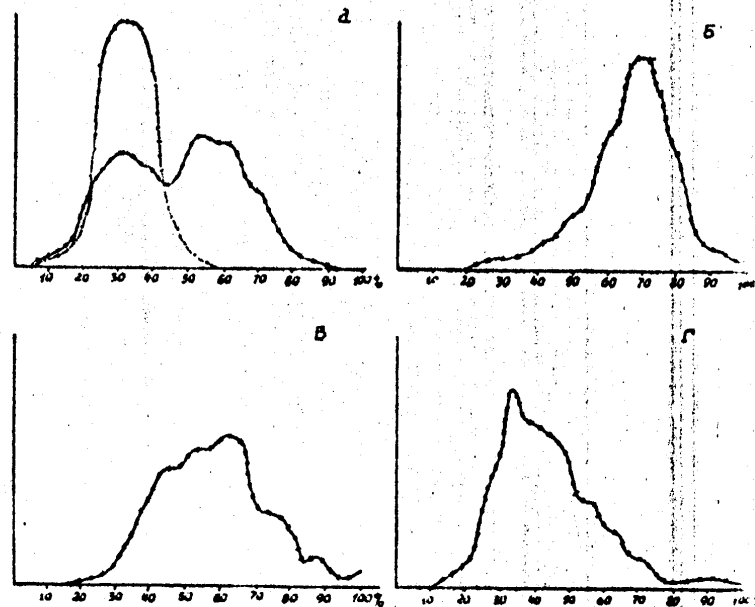


Fig. 4. Dynamics of curve distribution in the course of elaborating a defensive conditioned reflex in rabbit No. 1.

- a. Before elaboration of the conditioned reflex;
- b. After six pairings;
- c. After 66 pairings;
- d. After 99 pairings.

The solid line denotes the experimental distribution curve, and the dotted line the theoretical distribution curve.

type (rhythmic light, uninterrupted sound and uninterrupted light); electro-skin stimulation of the animal's hind paw was used as reinforcement.

The total background synchronism existing in the cortex of rabbit No. 1, before the conditioned reflex was elaborated, was characterized by a distribution curve shown in Fig. 4a. This curve has a maximum in the region of 33%, which indicates the presence in the cortex of a considerable number of independently working points. Apart from this maximum, there exists another maximum in the region of independent points, accounting for 56% of similarity. This is indicative of the existence in this rabbit of a considerable group of points with a positive interconnection. It can be seen from the distribution curve that there exist points providing a similarity to one another of potential oscillations, amounting to 70% or more. The group of such points forms a structure located in the frontal areas of the cortex (Fig. 5a).

The first pairings resulted in a very considerable increase in synchronism, which was expressed in an almost complete disappearance of independent points and in a sub-

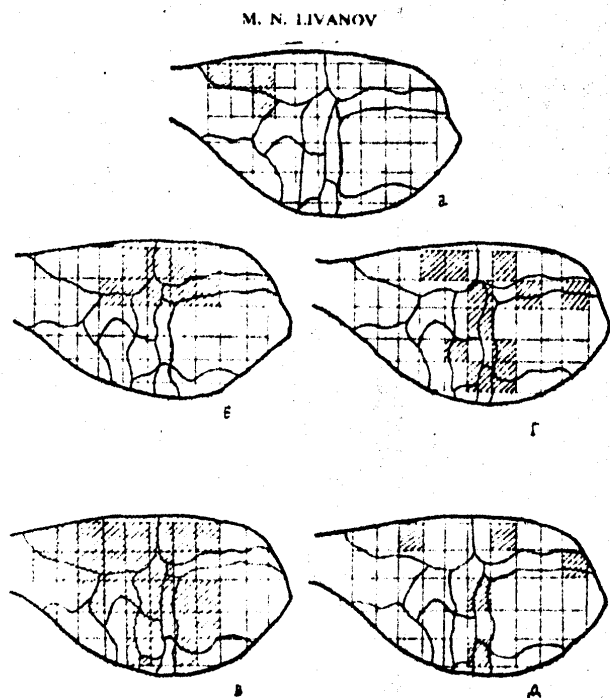


Fig. 5 Dynamics of distribution over the cortex in rabbit No. 1 of areas with a high degree of biopotential similarity (over 70%) in the course of elaborating a defensive conditioned reflex.

a. Before elaboration of the conditioned reflex;

b. After six pairings;

c. After nine pairings;

d. After 66 pairings;

e. After 99 pairings.

The boundaries of the cytoarchitectonic fields according to Rost are shown in the contour of the left hemisphere. The squares indicate schematically the region of location of the corresponding electrodes. The sections inside which correlation of the biopotentials is not below 70% are hatched.

stantial displacement of the whole group of positively interconnected points into the region with a higher percentage of similarity. The maximum of the distribution curve shifted to 73% (Fig. 4b). In response to a conditioned stimulus, individual points began to appear, which work absolutely synchronously among themselves, that is they produce 100% of similarity.

The structure with a high degree of similarity appeared in this case in the parietal region and it grew larger by the increase in the number of pairings, involving also adjacent areas of the cortex (see Figs. 5b and 5c). At this period there appear conditioned movements. This stage probably corresponds to that of generalization of conditioned activity.

Beginning with the ninth experiment (after 33 pairings), there is gradual weakening of synchronism. The shift of maximum from 73% to 60% of similarity indicates that

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total synchronism is decreasing. On the other hand, the existence of a second group of points which corresponds to a high percentage of similarity (maximum of 90%) testifies to the preservation of a certain group of points working with a very high percentage of similarity (see Fig. 4c).

In the course of further pairings, the displacement of the curve continued, tending to increase the number of independent points and to weaken gradually the total synchronism and to narrow the groups of points working with a high percentage of similarity.

Finally, after 99 pairings, the maximum of the distribution curve came close to the level of similarity (Fig. 4d).

The way these processes are distributed on the surface of the cortex is well demonstrated in the topographic pictures. Fig. 5d shows that after 66 pairings only individual areas of interconnected points remain in place of the large synchronous structure. These areas are separated by areas which were released from the structure and were working independently.

It is precisely at this stage that the conditioned reflex becomes regular.

Fig. 5e shows the topographic distribution of synchronism at the stage of a fully stable reflex. Only individual points located within the analysers participating in the elaboration of the conditioned reflex (i.e., in the motor, optical and acoustic regions) remain interconnected.

It can be seen from the above material that intensification of synchronous activity in the first stages of forming the conditioned reflex occurs by an extension of the area where the cortical elements work with a high degree of synchronism. This extension comes from the parietal regions, that is from the skin analyser, the cortical representation of the unconditioned reflex, and envelopes almost the whole hemisphere in its maximal development. The weakening of synchronous activity occurs through the release from the large structure of some areas with the preservation of others, the result being that individual remotely located but functionally connected areas of the hemisphere remain with a high degree of synchronism.

It becomes clear from the above that some distribution of the potential similarity along the surface of the hemisphere results from definite functional interrelations. We have then at our disposal methods which permit to study the functional architectonics of the cortex in its dynamics.

In her investigations, our associate I. N. KNIPE made an attempt to compare the synchronism of the bioelectrical activity of the cortex and of subcortical formations.

Changes in biopotentials were studied simultaneously in 25-30 cortical areas and 25-30 areas of various subcortical formations. Electrodes from 30 to 40  $\mu$  in diameter were implanted in groups of from six to eight electrodes, their recording ends being cut at various levels. The bioelectrical activity of various areas of the diencephalon (the reticular, medial and lateral nuclei of the thalamus and various parts of the hypothalamus) and of the mid-brain (the reticular formation and the substantia grisea centralis) was recorded.

The investigations have shown that the processes of synchronization are substantially weaker in the background biopotentials of various subcortical formations than in the cortex. This appears to reflect their considerable functional individualization. In accordance with this, the synchronism of the biopotentials is far more prominent at various points of one and the same subcortical formation.

As a defensive conditioned reflex is elaborated, synchronization of the biopotentials arises in subcortical centres, as well as in the cortex. The synchronization involves various subcortical formations.

The data so obtained warrant an interesting preliminary conclusion to the effect that the systems of synchronization appearing in the cerebral cortex and in subcortical centres,

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as a conditioned reflex is elaborated, prove to be basically independent of one another.

As a result of numerous investigations initiated by MAGOUN (1944, 1950), MORUZZI and MORALES (1949) and JASPER (1949), a conception arose regarding the specific and non-specific influences of subcortical centres on the cortex.

Apparently the possible existence of independent mechanisms of synchronization in the cortical and subcortical centres should not be excluded, along with the above influences. However, as a conditioned reflex is elaborated, some subcortical formations begin to be involved in synchronous activity with the cortical structures. This process covers only individual subcortical centres, without deranging the synchronous activity of subcortical formations, independent of the cortex. A further study of the above phenomena may considerably help in disclosing the importance and localization of various cortico-subcortical connections.

N. E. VEDENSKY, and later I. I. SPIK and A. A. UKHTOMSKY, have pointed out that the rate of increase in excitation in time and lability are one of the basic factors determining the spreading of the excitation process over the substrate.

UKHTOMSKY perceived in the factor of variable lability and in the capacity for establishing isolability the main condition determining the establishment of connections between the individual nerve centres of the brain. Synchronization of biopotentials is a direct indication of the similar course of the processes in time and, consequently, should reflect the mutual tuning of nerve structures, which ensures the possibility of their active interconnections.

In the light of these conceptions, the phenomena of synchronization of biopotentials, and their regularities and distribution acquire a special interest.



## SYNTHETIC PRINCIPLE IN SPACE FLIGHT PHYSIOLOGY

A. GURJIAN

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In the course of biological evolution human and animal organisms have become adapted to the conditions of their existence on Earth. The atmosphere of the Earth protects life against space hazards. The problem of the effects of space flight is a biological problem with many aspects. The solution of the problem involves, besides methods of physiological investigation, different biological methods and various biological objects representing the organic world in different lines and stages of evolution.

It is difficult to detect some features of the effects of flight in a multicellular highly organized animal. Thus, local injuries of some separate cell groups caused by the heavy particles of cosmic radiation may remain unrevealed due to compensatory and regenerative processes. It can be assumed that fertilization of the ovum, the development of the embryo as well as some functions of the subcellular structures adapted to the conditions of the terrestrial gravitational field will alter during the flight. The study of such problems should involve microbiological and cytological objects. They are convenient from the methodological point of view and they allow us to obtain a statistically large sample in a short time.

This is why the experiments in satellite space ships involved such biological objects as mammalia (dogs, mice, rats, guinea pigs), insects, plants and many microbiological and cytological objects at tissue, cellular, subcellular and molecular levels. It was the execution of the broad program of biological investigations in satellite space ships that proved the security of a manned flight and paved the way for GAGARIN's and TITOV's first space flights.

The physiological examination of space flights requires a wide biological approach (SISSAKYAN, N. M., GAZENKO, O. G., GHENIN, A. M., 1961; ZHURIN-VEREJNIKOV, N. N., 1961). During space flights the organism is influenced by many factors which are unusual in their physiological effects. Some of them are known comparatively well, others inadequately (lasting weightlessness, cosmic radiations etc.).

Of utmost importance is the fact that many flight factors act in complex combinations. The influence of the complex affecting the organism in space flight has its own characteristic features in addition to the individual effects and it is difficult to predict these when examining the components of the complex separately in laboratory conditions.

The peculiarity of the physiological responses to accelerations and weightlessness following each other had already been noticed in the experiment with Laika in the second sputnik. When the acceleration (active stage of flight) was over the physiological state of the blood circulation and the respiration of the animal in weightless condition became normal much later than in laboratory conditions where the space flight acceleration was followed not by weightlessness but by the terrestrial gravitational field (CHERNOV, V. N. and YAKOVLEV, V. I., 1958; PARIN, V. V., YAZDOVSKY, V. I., 1961). The problem of the resistance of the organism to negative accelerations connected with the return

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of the astronaut to Earth after a prolonged period of weightlessness causing deadaptation of vascular and other systems evoked great anxiety. H. Beck *et al.* (1959) devoted much attention to the characteristics of the physiological response to the effect of accelerations and weightlessness following each other.

Of great importance is the problem of the combined effects—ionizing radiation (particularly cosmic) and other flight factors. Changes in radiosensitivity (genetic effect in particular) as well as alterations in resistance to other effects, such as mechanical accelerations, vibrations and weightlessness, are probable. To estimate the expected biological effect of space flight one should consider the sequence and durations of particular factors (among them various kinds of ionized radiation in different space zones).

Biological experiments in space ships revealed a number of moderate genetic and histological alterations. The character of these alterations differed in certain features when compared to the effect of ionizing radiation. Laboratory experiments on vibration effects reproduced only to a certain degree and only some features of the data obtained in the flight (ARSENYEVA, M. A., ANTIPOV, V. V. *et al.*, 1961; GLEMBOTSKY, Y. L. *et al.*, 1961; PARFENOV, G. P., 1961). These results confirm our considerations referring to the specific characteristics of the combined effects of radiation, acceleration, weightlessness, vibration, barometric pressure, gas composition and others which have not yet been adequately examined.

All this requires a broad consideration of space flight conditions: various external factors of the flight and life conditions in the space ship cabin (nutrition, water supply, air regeneration, regime of work and rest, sanitary accommodation, etc.), which will influence the astronaut. The individual characteristics of the astronaut (sex, age, radiosensitivity, sensitivity to mechanical factors) are also very important.

It is so far impossible to reproduce some of the factors of space flight in laboratory investigations (e.g., lasting weightlessness), as well as their particular components (e.g., heavy particles of primary high energy cosmic radiation). Moreover it seems impossible to reproduce the complicated content of particular factors (spectrum of vibration frequencies, profile of gravitational changes, the complicated composition of ionizing radiation, perpetual changing in space and time) and all the space flight factors in complex combination.

This is why the carrying out of biological and, in particular, physiological experiments in satellites and ships is a necessary link in the study of the biological effects of space flight. No computations and extrapolations can substitute for biological tests on animals in flight, preceding every new variant of a manned flight. The analyses and thorough examinations of the material obtained in flights, the perfection of methods as well as the realization of control experiments require, however, wide laboratory investigations. It brings us to the conclusion that flight and laboratory experiments should harmoniously contribute to each other.

Examining space flight also influences the physiology of particular organs and systems, the investigator will unavoidably come to the consideration of the organism reaction as a unity in which all the parts are in close interaction.

Considering the physiology of weightlessness, it can be assumed that the altered reception of the vestibular analyzer will cause alterations of other analyzers and afferent systems of the organism: alterations of the oculomotor apparatus and vision, of postural reflexes and muscle tonus, movement coordination, internal organ functions and other systems of the organism (YUGANOV, E. M., KASSYAN, I. I. *et al.*, 1960, 1961; YAZDOVSKY, V. I., YUGANOV, E. M., KASSYAN, I. I., 1961; GRAIBILL, 1952; GIERATHEWOHL, 1957; GIERATHEWOHL and STALLINGS *et al.*, 1958).

The basis of the reactions of the total receptor system is the interaction principle of

## A. GURJIAN

afferent systems, the universality of which was proved by academician L. A. ORBELI (1934, 1948), his pupils and followers.

We mean here interactions within a sense organ (analyzer) and between particular analyzers as well as the reaction of the analyzers taken as a whole and defined by the conception of the 'functional systemicity in the work of the analyzers' (KOMENDANTOV, G. L., 1959; GAZENKO, O. G. and YAZDOVSKIY, V. I., 1961). The relations of the rod and cone visual reception, otoliths and semicircular canals, various parts of the otolithic apparatus, tactile and pain sensibility can serve as examples of interaction within a sense organ (LIBEDINSKIY, A. V., 1936, 1938; KHILOV, K. L., 1952; LANSBERG, M. P. *et al.*, 1960).

In this respect the physiology of weightlessness should be understood above all as the investigation of a disturbance of the usual interaction complex of the afferent systems causing shifts in the central nervous system and, in particular, in the cortex, which can affect the activity of internal organs (Bikov, K. M., 1947). On the other hand, the altered sensory response of internal organs in the weightless state may greatly influence the cortex (AYRAPELIANTS, E. SH., 1952, 1960; CHERNIGOIISKY, V. N., 1960).

The autonomic and particularly the sympathetic nervous system will also play an important role in space flight physiology. The universal adaptive-trophic influence of the sympathetic nervous system, in particular on receptors and the afferent system, was profoundly and systematically examined by academician L. A. ORBELI and his school. In this respect the adaptive-trophic functions of the cerebellum in dominating the afferent nervous system are very important in the physiology of the central nervous system (ORBELI, L. A., 1934, 1948; GHINEITSINSKY, A. T. and LIBEDINSKIY, A. V., 1947; ALLENANIAN, A. M., 1948).

The great reduction of sensory information in space flight as well as the unusual demands on the astronaut's higher nervous activity (emotional, psychological strain, rhythm of sleep and waking, singularities in mental and physical work) will no doubt strongly affect his nervous system functions. In addition, of great importance are alterations in the humoral systems of the organism: metabolism, the activity of inner and outer secretion, etc., which are closely related to the functions of the central nervous system (GURJIAN, A. A., DEMIN, N. N., KORNEVA, N. V., LVOVA, T. S., TUTCHIKINA, E. T., USPENSKAYA, M. S., FEDOROVA, T. A., 1961).

Local cell injuries and failure of functions as well as the general effect of ionizing radiation on the central nervous system, and, in particular, on higher nervous activity may occur under the influence of cosmic radiation particles and of the roentgen and gamma rays (LIVSHITZ, N. N., 1961).

The enduring of a lasting space flight is an important physiological problem and involves the adaptation and compensation of functions altered in space flight. A reorganization and new coordination of afferent systems, a new 'functional systemicity in the work of analyzers' will take place in space flight. A profound knowledge of the physiological mechanisms of their reorganization will allow us to foresee the effects of flights of various duration. It will allow us to predict in what conditions and when the necessary adaptation and reorganization will occur and in what circumstances the accumulation of unusual effects will lead to a failure of the adaptation and compensatory mechanisms of the organism.

The examination of this problem of space physiology will greatly contribute to the establishment of rational flight programmes and measures influencing certain links of adaptation and compensatory processes (for example, the use of the great stock of neuro-tropic remedies).

We consider that I. P. PAVLOV's synthetic principle which considers the many sided

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organism response to the complex of the external world as a unity should be the basis of space flight physiology study.

##### *Summary.*

The problem of the effects of space flight is a biological problem with many aspects. The solution of this problem involves different biological methods and various biological objects representing the organic world in different stages and lines of development.

The influence of factor complexes affecting man in space flight (simultaneously or in various sequences) has its characteristic features which are difficult to predict by studying them separately in the laboratory (acceleration-weightlessness, weightlessness-acceleration, vibrations, acceleration-cosmic radiation, etc.).

Data received in space flight should be physiologically analysed, comparing them with laboratory data concerning the effect of separate factors or groups of factors.

In examining space flight effects on the physiology of particular organs and systems, one should consider the organism as a unity in which all parts are in close interaction (interaction of sense organs, neuro-psychic and somatic spheres, somatic and autonomic nervous systems).

I. P. PAVLOV's synthetic principle, academician L. A. ORBELI's teaching of the interaction of afferent systems and of the trophic role of the sympathetic nervous system, as well as the works of academician K. M. BIKOV's school on the interaction of the external and internal organs can greatly contribute to the examination of space physiology.

The enduring of a lasting space flight is conditioned by adaptation resources and mechanisms, and by the compensation of functions altered in space flight conditions. The knowledge of compensation mechanisms allows us to foresee the consequences of different flights, work out a rational flight programme and influence certain links of the compensation process (e.g., drugs).

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## INFORMATION PROCESSING IN THE NERVOUS SYSTEM

inhibited by Group I volleys from flexor muscles; Group Ib afferent fibres of muscle by Group I volleys from both flexor and extensor muscles; the afferent fibres giving the flexor reflex (cutaneous and Group II and III muscle afferent fibres), are inhibited by all the afferent fibres, both cutaneous and from muscle. Presynaptic inhibitory action on the flexor reflex afferents (FRA) and on Group Ib fibres, but not on Group Ia fibres, is very effectively produced by brief repetitive stimulation of the sensorimotor cortex, and also of some other localized areas of the cortex. Presynaptic inhibition provides a mechanism for suppressing sensory input before it has exerted any synaptic action. In many situations it provides a negative feed-back control of sensory input, e.g. FRA impulses depress the reflex actions of all types of FRA input, so that any powerful FRA input will suppress all trivial inputs. However, no functional meaning can yet be ascribed to some varieties of presynaptic inhibition.

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Junctional transformation primarily depends on the synaptic arrangement of neurons. Convergence and divergence are the main principles of neuron coupling, but both are generally combined in the CNS. Linear arrangement—i.e., 1:1 ratio between presynaptic and postsynaptic elements—although rare, occasionally occurs, for example in the central auditory pathways and in the ciliary ganglion of birds and higher mammals. Without a single exception these synapses are of the basket- or caliciform type, so that their contact surface is extraordinarily large. Comparison of a great many different synapse types reveals that size of contact surface, both in the individual contact and in the total contact between two neurons, is inversely related to the amount of convergence upon the postsynaptic neuron. Histological evidence will be presented for the assumption that the safety factor of the synapse is greater the larger the surface of contact. This generalization may help to identify histologically synapses of different pathways impinging on the same neuron.—It is difficult to correlate anatomical and physiological properties of the synapses until the functional significance of axo-somatic versus axo-dendritic contact is better understood. The large posterior horn neurons of the spinal cord are cited as an example, where this question becomes very relevant to the topic of the discussion. These neurons receive axo-somatic contacts (boutons terminaux) from primary afferents and from various descending pathways. Their dendrites, being embedded into the gelatinous substance of Rolando, are subjected—very much like the dendrites of the cerebellar Purkinje neurons—to axo-dendritic synaptic influences of exceedingly large convergence. It would be highly interesting to know whether the neurons of the gelatinous substance—where there are no other pathways conducting outwards—only modify the threshold of the large posterior horn neurons, or conversely can induce them to discharge. This is probably one of the key-points in the transformation of information at the junction between primary and secondary sensory (especially cutaneous) neurons.—Attempt to identify histologically inhibitory synapses are briefly touched upon. New information gained with the electron microscope is briefly summarized.—Attention of neurohistologists and neurophysiologists has been focused until now almost exclusively upon the usual type of synaptic junctions in which contact is simply effected by close opposition of presynaptic and postsynaptic surfaces. There are, however, at least two other possibilities of more complex arrangements: (1) 'Interposed' synapses, in which a fine—also presynaptic—terminal is sandwiched between two larger synapsing surfaces, and (2) 'superimposed' synapses, in which the superposition of a presynaptic terminal upon another larger pre- or postsynaptic terminal is seen. A very characteristic example of the first type occurs in the cerebellar cortex, where the main synapses between the granule neuron dendrites and the mossy fibers are pervaded by the fine meshwork of the large Golgi

# INFORMATION PROCESSING IN THE NERVOUS SYSTEM

cell axon ramifications. The fine terminal branches of this meshwork are really engulfed by the large contacting surfaces of the main synapses. Since the Golgi cells are axodendritically activated by the parallel fibre system, and axo-somatically by the collaterals of the climbing fibers, this type of synapse closes one of the two intrinsic feedback circuits of the cerebellar cortex, simultaneously combining it with the strictly channeled olivary inflow. The second type is frequently observed in electron microscopic pictures of different synaptic regions, although the interpretation of such findings is rather difficult. A fairly good example of this type is seen in the large caliciform synapses of vestibular receptors, in which smaller, most probably presynaptic, terminals can be seen on the postsynaptic calices. It would be extremely interesting if these secondary synapses could be identified as the terminals of efferent fibres, which would control the input from the receptors. Similar secondary or superimposed synapses can be observed also in other systems, especially in the lateral geniculate body, where there is fairly good evidence for considering them as terminals of cortical feedback pathways. Recent observation of interaction between presynaptic elements—as supposed to be the cause of 'presynaptic inhibition'—probably even on sites 'upstream' relative to the synapse, calls for a thorough microscopical and electron microscopical analysis of such and similar hitherto unknown or neglected types of synaptic arrangements.

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The functional relation between the input and output of any given neuronal central unit depends on an array of factors. Of these the specific properties of the connecting prefibers is obvious, but the location of these connections on the unit has, in a number of cases, also important effects on the output. Examples of the latter will be presented and the special case of crustacean interneurons with input terminals at a number of widely separated locations will be more fully analyzed.

In addition, examples will be discussed demonstrating how nerve cells differ from each other in such aspects as maximum firing frequency, adaptation rates, and the like. These intrinsic factors, though varying with the previous history of the activity of the unit, are, nevertheless, just as fixed for specific types of units as are the patterns of their anatomical connections—at least in arthropod nervous systems. As a result, a great deal of order can be found at the single unit level.

It is not unreasonable, therefore, to hope that eventually in systems of this kind a knowledge of both the intrinsic properties of the units and their patterns of input connections will lead to a considerable degree of predictability of the total output.

Favorable factors for such an approach in arthropods are the limited number of central units and the presence in most of long central neurons in which impulse traffic forms the only means of communication.

## SESSION IV

### PATTERN RECOGNITION, SET (PERIPHERAL AND CENTRAL)

*Chairman: Y. ZOTTERMAN*

Y. ZOTTERMAN, Department of Physiology, Veterinärhögskolan, Stockholm 51, Sweden  
Paper not submitted.



## INFORMATION PROCESSING IN THE NERVOUS SYSTEM

*Discussants*

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Paper not submitted.

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Single neuronal activity was recorded by conventional techniques from somatosensory area I, the midbrain reticular formation and the cuneate nucleus of cats in separate experiments. The data were stored on magnetic tape and were later analysed electronically.

The interspike interval distributions of area I and reticular neurons are complex. Those cortical neurons which gave a sustained discharge in the absence of applied peripheral stimuli ('spontaneous activity') yielded a peak near the brief interval end of the interspike interval distribution, or showed a peak in the intermediate portion of the distribution, with a prolonged drop off towards the long interval end. Analysis of spontaneously firing reticular neurons showed that the distribution is not well represented by Poisson-distributed random discharges. Furthermore, determinations of the interspike interval probability distributions as a function of the immediate past history of unit activity showed that the length of a given interspike interval is strongly dependent on the length of the immediately previous interval.

Sustained, evoked activity at a primary somatosensory relay was studied to provide leads in building a model of higher level interval distributions. Slowly adapting primary axons recorded superficial to the cuneate nucleus show a regular discharge pattern following appropriate positioning of the limb. By contrast, postsynaptic cuneate neurons show a variety of discharge patterns ranging from a rhythmic pattern with greater dispersion of the interspike intervals than is shown by afferent fibers, to irregular discharge patterns produced by near maximal peripheral stimulation. Two biological models are suggested to account for such irregularity: (1) asynchronous bombardment of the cuneate neuron by two or more afferent fibers with different regular periodicities. (2) Intermittent failure of synaptic transmission which occurs at high afferent fiber discharge rates.

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There have been several attempts to express the rather complicated neuronal impulse activity of the central nervous system by means of mathematical formulae and/or physical concepts in order to investigate its behaviour or to establish a model.

One of the possible ways utilizes the classification of the neuronal impulse activity and its symbolic notation by means of elementary formulae. These can be derived from the basic one  $\alpha' = (1 - \alpha) x$  by all possible modes of the complementation both of afferent variables  $\alpha$ ;  $x$  and the efferent variable  $\alpha'$ . To each of the eight expressions so obtained there corresponds some elementary 'ideal' impulse neuronal activity.

It is very improbable that the transformation carried out on certain living neuronal structures, determined, e.g., by measurement, can be expressed or identified with some of these elementary formulae. However, a suitable choice of combinations and/or iterations of elementary formulae enables us to approximate to a given activity.

On the other hand, to each of these more complicated expressions there corresponds a



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more involved structure or activity which can be considered as a generator of the given expression.

Some other consequences are indicated and relations to other theoretical fields established.

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In the early fifties it was established that man would, in a variety of situations, react to signals with a delay proportional to the information conveyed by the signal. This suggested that the nervous system was acting in these cases as a single channel of limited capacity. More recent results have however shown that with very highly practiced relationships between stimulus and response, the time taken to react becomes independent of the information conveyed by the signal. Such results are less easily interpreted in terms of a noise-free channel, than they are in terms of a decision mechanism acting on noisy signals. At high levels of practice the noise level may then be regarded as being reduced.

On either theory the crucial function performed by the brain is discrimination between members of a set of alternative stimuli; and the relations between the actual stimulus and others not now present become crucial. Furthermore, on either view man is likely to be selective in his response, because of his limited capacity, and there are interesting differences between alternative ways in which he can do this.

## SESSION VI

## INFORMATION STORAGE

*Chairman:* H. H. JASPER

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The firing patterns of individual cortical neurones can now be recorded with indwelling microelectrodes in normal unanaesthetized animals, awake or during normal sleep, and while responding to physiological stimuli during conditioning experiments. Examples of the sound of such patterns from the cortex of the monkey will be presented from records taken on magnetic tape during conditioning experiments.

Most cells within the brain show 'spontaneous' activity independent of deliberate sensory stimulation, even in sensory receiving areas when the animal is at rest, or even asleep in a dark, sound-proof room. Firing patterns are irregular, but not strictly random. Over-all frequencies range from once in 5-10 seconds to rates of 50-100 per second, the higher rates usually being maintained for short periods of time. Under certain conditions of drowsiness or sleep, some cells fire in brief bursts of higher frequency discharge (200-300 per sec.) separated by quiet intervals. At times the burst frequency may be regular at about 3 to 10 per second, in relation to the rhythm of the 'brain waves'. Arousal of the animal from sleep or to increased vigilance has a profound general effect upon firing patterns of cells in all cortical areas studied, spontaneous activity being reduced in many together with increased responsiveness to discrete stimuli, resulting

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One of the more general questions which can be precisely formulated and investigated within this framework is the following: What proportion of the system's effort at a time should be spent in acquiring and processing new information and what proportion should be spent manipulating known aspects of the environment? It can be shown under certain conditions of physical interest, that the effort should be divided approximately equally between the two tasks.

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If an animal is confronted with a certain differentiation problem, i.e., it has to react differently to various cues presented to it according to a definite programme, there is usually not one but two or more solutions to such a problem. For instance, let us try to establish a simple differentiation between two similar exteroceptive stimuli  $S_1$  and  $S_2$  by reinforcing  $S_1$  and not reinforcing  $S_2$ . Let us suppose that these stimuli are applied according to the following schedule, often used in the C.R. practice:  $S_2$  follows a variable number of  $S_1$  applications, is never given at the beginning of a session, and never repeated twice in succession. After some time the animal learns to react appropriately to each stimulus, and it is tacitly admitted that this is due to memorizing and discerning the absolute values of  $S_1$  and  $S_2$ . However, it is easy to notice that in such a training the animal may also learn that any stimulus within a given modality repeated several times in succession is positive, while a *different* stimulus, whatever it is, is negative. In other words, the animal may learn not to discern the absolute values of both stimuli, but only grasp their disparity by a recent memory mechanism. By appropriately modifying the experimental procedure it is possible to reveal which way of learning the animal actually uses.

A number of examples of such an analysis of various forms of differentiation are presented. The old concept of animals making 'hypotheses' is reevaluated, and the hierarchy of 'hypotheses' particular for a given species is indicated. It is shown that the way which the animal adopts in the solution of a given differentiation task throws some light on the functional organization of its brain.

## Discussants

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If it be agreed that the behavior of a cat differs in important ways from the behavior of a dog, then it follows that the brains of the two species differ significantly also. The nature of this difference, the genetic mechanisms at work, and the cellular elements through which the genetic information is conveyed (neurons, glial cells, or both) remain however obscure. Experimental evidence drawn from the literature pertaining to these problems will be discussed.

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